Prenatal and Perinatal Infection and Schizophrenia

Prenatal infection and mediators of inflammation during **pregnancy** and the **perinatal** period are associated with increased risk of **schizophrenia**.

General Information	
Broad Focus Area	Neurodevelopment and behavior
Background and Justification	Schizophrenia is a severe psychiatric disease typically appearing in late adolescence or early adulthood. It is associated with significant long-term morbidity, occupational disability, social disadvantage, and high mortality from suicide and other causes. The burden of the disease extends to the family, for whom there are major economic and social implications. Converging evidence suggests that many cases of schizophrenia are neurodevelopmental in origin, that both genes and environment play a role in the etiology of these cases, and that exposures in early gestation may be linked to schizophrenia, in particular, infection and nutritional deficiency.[1,2] In recent data from long term follow-up of participants in the US Collaborative Perinatal Project (an NCS-like longitudinal study performed in the US in the 1960s), levels of maternal pregnancy serum immunoglobulins (IgG and IgM) were associated with increased risk of schizophrenia in offspring, suggesting that maternal infection increased the risk of schizophrenia among children from those pregnancies.[4] Evidence that increased exposure to mediators of inflammation in utero is associated with higher risk of schizophrenia has also been reported.[5] Furthermore, levels of specific antibodies were examined for a variety of infectious agents and only elevations of antibodies to herpes simplex virus, type 2 (genital herpes), were associated with increased risk of schizophrenia.[4] While infectious agents have been suspected of increasing the risk of schizophrenia, their role has not been established.[3,4,5] Herpes simplex viruses are known to cause encephalitis in infants,[6] thus latent effects of less severe infection are biologically plausible. Investigation into effects of early exposure to herpes simplex type 2 is timely given the recent increase in prevalence of infection among young adults in the United States, where over 20% of the population aged 12 or more years is now seropositive.[7] While other infectious agents are also suspected of increasing risk, the data for herpes provides a specific example for investigation.
Prevalence/ Incidence	By age 21, approximately 0.3% of the population develops schizophrenia,[8] and thereafter the cumulative incidence increases to approximately 1.0%.[9] In term pregnancies, about 1-2% are affected by chorioamnionitis (intrauterine infection); in pregnancies ending in preterm births, the prevalence of such infection is higher.[10] Results of a nationally representative study show that genital herpes infection is common in the United States. Nationwide, one out of five adolescents and adults ages 12 and older have had genital HSV infection. Genital HSV-2 infection is more common in women (approximately one out of four women) than in men (almost one out of five).[11] Antibodies to HSV-2 have been detected in approximately 20 percent of pregnant women; however, only 5 percent report a history of symptomatic infection.[12] The prevalence of HSV excretion from the genital tract of women who are pregnant at term is estimated to be between 0.3 and 1.9%.[13]
Economic Impact	The annual cost of schizophrenia in the United States was recently estimated at

	$65.2 billion,[14] and a substantial portion is due to disease in young adults.[15] About two thirds of those who develop schizophrenia continue to be affected throughout adulthood.[3]

Exposure Measures			Outcome Measures	
Primary/ Maternal	Maternal infection/inflammation: - Infection serology (lymphocytes, antibodies, cytokines/interleukins, inflammatory markers) - Cultures (cytokine; metalloproteinase) - Maternal hormones/cortisol - Medical history of fever and recent infection (medicine usage) - Dental exams		***Primary/ Child***	Schizophrenia diagnosis
Methods	- Blood samples - Vaginal/cervical cultures - Examination by a medical professional - Interview		Methods	Examination by a medical professional (neurological and psychological testing, neurological and psychological function development, social function)
Life Stage	Repeated prenatal: all three trimesters and at birth		Life Stage	Years 5, 10, 15, 20
Primary/ Child	Prenatal infection/inflammation: - Infection serology (lymphocytes, antibodies, cytokines/interleukins, inflammatory markers) - Umbilical cord/placental culture (antibodies; cytokines)		***Secondary/ Child***	School performance - School grades
Methods	- Amniotic fluid analysis - Umbilical cord blood culture/pathology		Methods	School record review
Life Stage	Birth		Life Stage	Years 5, 10, 15, 20
Secondary/ Maternal	Maternal infection/inflammation			
Methods	Medical record review			
Life Stage	Enrollment, all trimesters, years 5, 10, 15, and 20			

Important Confounders/Covariates	
Age	Schizophrenia is typically a disease that manifests itself in late adolescence or early adulthood. Men tend to have earlier onset (early to mid 20's) than women (late 20's). Early childhood onset may have unique risks. [23]
Economic, race, ethnicity status	Schizophrenics tend to be of a lower socio-economic class. However, like many mental illnesses, this may be that the symptoms of the disease themselves cause a drift into a lower class or because the hardships of a

	lower economic class causes stress and triggers the disease. Schizophrenia has similar prevalence rates around the world, although there is discussion that African Americans are over diagnosed in the U.S.[16]
Family History of Mental Health	Schizophrenia has been shown through family, sibling, and twin studies to have a genetic component. [1]
Residential Environment	Country living under the age of 16 is negatively correlated with the incidence of schizophrenia. It is estimated that 34.6% of schizophrenia cases would be prevented if persons were not raised in the city.[16]
Smoking status	Rates of smoking by schizophrenics are about 66-88%,[17] 2 to 3 times that of the general population. Smoking usually starts at an average adolescent age before diagnosis. [18]
Medications	Street drugs taken during pregnancy, including marijuana, PCP, methamphetamines, increase the risk of schizophrenia [18]
Systematic infections	There is some evidence that children with post natal systematic infections, particularly central nervous system infections, are 4.8 more times as likely to develop schizophrenia.[19]
Vaccinations	Vaccinations may be a plausible option for prevention of schizophrenia by reducing the rate of prenatal infection.[20]
Nutrition and Diet	A recent Finnish study hypothesized that poor nutrition, but not lower caloric intake, in utero and in early childhood is an increased risk factor for schizophrenics.[21]
Gestational age, weight, head circumference	Schizophrenics are more likely to be premature and have a low birth weight, although some argue that weight is merely a proxy for age and vice versa.[22]

Population of Interest		Estimated Effect that is Detectable
All children		Assuming 100,000 children are followed to age 21, and an exposure prevalence of 10% (e.g., for herpes simplex type 2), the smallest detectable relative risk is 1.6.

Other Design Issues	
Cost/Complexity of Data Collection	- While a simple examination of maternal antibody titers would advance the science in this area, consideration of the timing of the infection in relation to birth would be useful, which would require multiple blood samples during pregnancy. - Collection of swabs of the lesions for viral culture would enable an evaluation of the timing and rate of viral shedding in relation to subsequent schizophrenia. - In addition, ascertainment of schizophrenia among children born into the NCS could rely on reports of clinical diagnosis, or, for a more sensitive assessment of outcome, could employ screening questionnaires aimed at identifying subjects with lesser degrees of illness, that would be more completely defined in targeted follow-up of those who were screen-positive. - Because schizophrenia is generally not diagnosed until the late teens or early twenties, response and retention rates of NCS

	participants will be important for assessing this hypothesis.

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